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December 10, 2004

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APPLICATION NUMBER: ***60/530,822***
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Date of Deposit: December 18, 2003

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(b)(2).

		Docket No. 1529/2011	Type a plus sign (+) inside this box→	+

INVENTOR(S)/APPLICANT(S)

LAST NAME	FIRST NAME	MIDDLE INITIAL	RESIDENCE (City and either state or foreign country)
Hubschwerlen	Christian		France
Specklin	J.	L.	France
Baeschlin	Daniel	Kaspar	Switzerland
Sigwalt	Christine		France

TITLE OF THE INVENTION (280 character maximum)

Oxazolidinone-Quinolone Hybrid Antibiotics

CORRESPONDENCE ADDRESS

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STATE	MA	ZIP CODE	02199	COUNTRY	U.S.A.

ENCLOSED APPLICATION PARTS (check all that apply)

X Specification Number of Sheets 42
__ Figures Number of Sheets __ X Other (specify): Express Mail Label No. EV242754824US

METHOD OF PAYMENT

X	A check or money order is enclosed to cover the Provisional Filing Fee	PROVISIONAL FILING FEE AMOUNT ($)	$80.00
__	The Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number:		

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

X No. __ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,

Date: December 18, 2003 SIGNATURE: 

Customer Number: 29932 NAME: Paula Campbell Evans Registration No.: 32,503

Additional inventors, if any, are being named on separately numbered sheets attached hereto.

PROVISIONAL APPLICATION FILING ONLY

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Atty. Docket No.: 1529/2011 **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Hubschwerlen, et al.
Serial No.:	Not Yet Assigned
Filed:	December 18, 2003
Entitled:	Oxazolidinone-Quinolone Hybrid Antibiotics

CERTIFICATE OF MAILING UNDER 37 CFR 1.10

I hereby certify that the paper (and any paper or fee referred to as being enclosed) is being deposited with the United States Postal Service using Express Mail to Addressee Service, under 37 C.F.R. Section 1.10, **Express Mail Label No. EV242754824US** on this date, **December 18, 2003**, postage prepaid, in an envelope addressed to Mail Stop Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Nancy Arsenault
Name of Person Mailing Paper

Signature of Person Mailing Paper

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TRANSMITTAL LETTER

Enclosed for filing in the above-identified provisional patent application, please find the following documents:

1. Cover Sheet for filing Provisional Application;
2. Provisional Patent Application Specification;
3. Check in the amount of $80.00 for the requisite filing fee; and
4. Return Post Card.

Pursuant to 37 C.F.R. §1.27, Applicant claims small entity status.

The Commissioner for Patents is hereby authorized to charge any additional fees or credit any overpayment in the total fees to Deposit Account No. 16-0085, Reference No. 1529/2011. A duplicate of this transmittal letter is enclosed for this purpose.

Respectfully submitted,

Date: December 18, 2003

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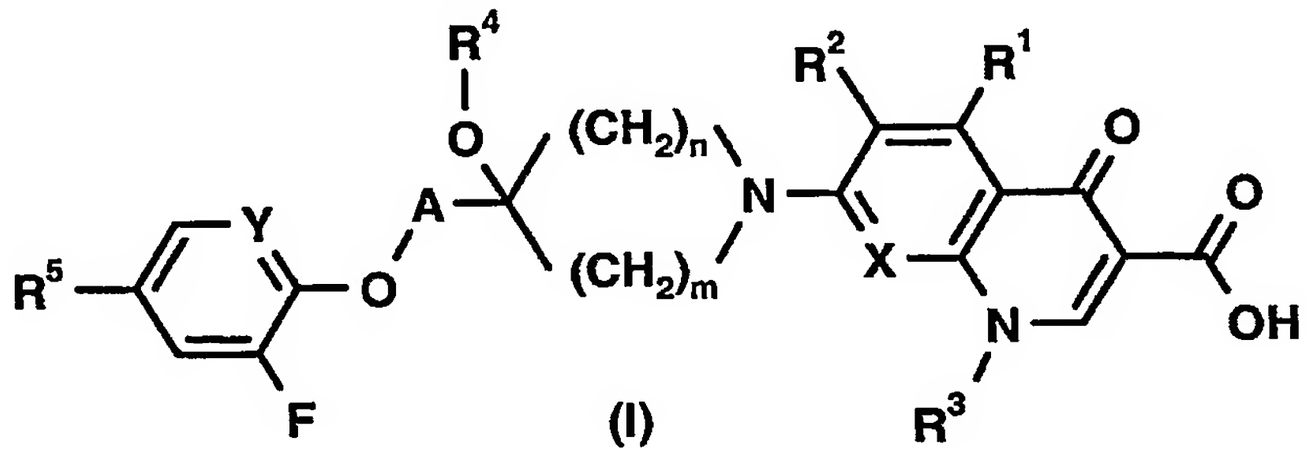
Docket No.: 1529/2011
Express Mail No.: EV242754824US
Date of Deposit: December 18, 2003

Oxazolidinone-quinolone hybrid antibiotics

The present invention describes new compounds in which the pharmacophores of quinolone and oxazolidinone are linked together through a linker that is stable under physiological conditions and a pharmaceutical antibacterial composition containing these compounds. These dual action compounds are useful antimicrobial agents effective against a variety of human and veterinary pathogens including Gram positive aerobic bacteria such as multiple-resistant staphylococci, streptococci and enterococci as well as Gram negative bacteria such as Moraxella catarrhalis and Haemophilius influenza and anaerobic organisms such as bacteroides spp. and Clostridia spp. species and acid-fast organism such as Mycobacterium tuberculosis, Mycobacterium avium spp.

Oxazolidinone-quinolone hybrid antibiotics have already been described (WO02059116, WO03002560, WO03031443, WO03032962). The major drawback of the compounds known in the state of the art is the poor water solubility, which makes the development of a formulation difficult.

The present invention provides new compounds of formula (I) with increased water solubility, that are useful antimicrobial agents and effective against a variety of multi-drug resistant bacteria



(I)

wherein

A is a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{2-4} alkynylene group or a C_{1-4} heteroalkylene group, all of which may be substituted by one or more hydroxy or amino groups;

X is CR^7 or N;

Y is CR^6 or N;

n is 1, 2 or 3;

m is 1, 2 or 3;

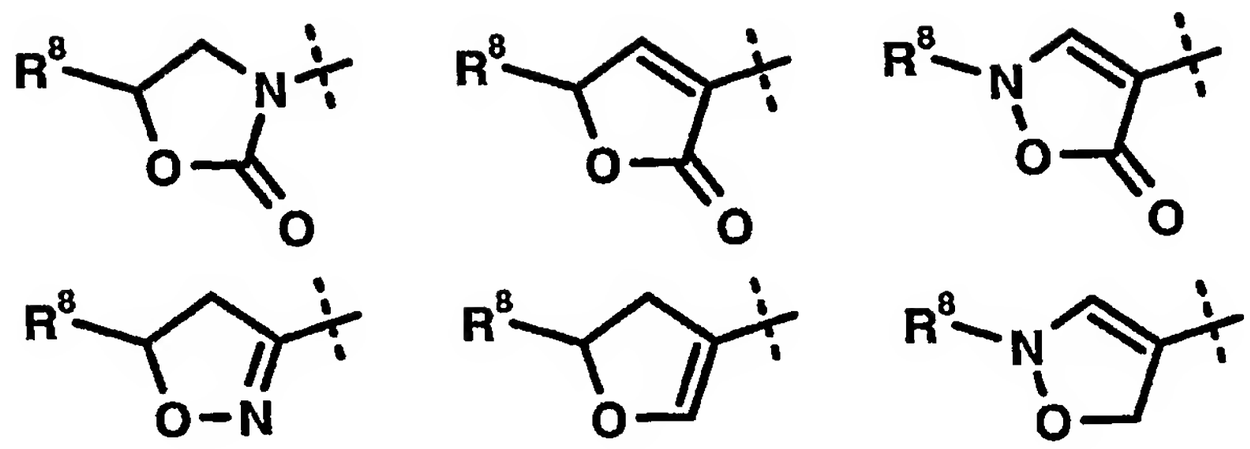
R^1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group;

R^2 is H, F or Cl;

R^3 is H, an alkyl group, an alkenyl group, an alkinyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl group, an alkylaryl group or a heteroarylalkyl group; all of which may be substituted with one, two or more halogen atoms like F or Cl.

R^4 is hydrogen, a group of formula $PO_3R^9{}_2$ or SO_3R^{10} or a heteroalkyl group carrying at least one OH, NH_2, SO_3R^{10}, PO_3R^9 or COOH group, wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl.

R^5 is selected from following groups:



R^6 is H, F, Cl or OMe;

R^7 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or

R^3 and R^7 can be linked via an alkylen, an alkenylen or a heteroalkylen group or be a part of a cycloalkylen or heterocycloalkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl; and

R^8 is a C_{1-6} heteroalkyl or a heteroarylalkyl group;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof.

It should be appreciated that certain compounds of formula (I) or (II) mentioned below may have tautomeric forms from which only one might be specifically mentioned or depicted in the following description, different geometrical isomers (which are usually denoted as cis/trans isomers or more generally as (E) and (Z) isomers) or different optical isomers as a result of one or more chiral carbon atoms (which are usually nomenclatured under the Cahn-Ingold-Prelog or R/S system). Further, some compounds may display polymorphism. All these tautomeric forms, geometrical or

optical isomers (as well as racemates and diastereomers) and polymorphous forms are included in the invention.

The term alkyl refers to a saturated or unsaturated (i.e. alkenyl and alkinyl) straight or branched chain alkyl group, containing from one to ten, preferably one to six carbon atoms for example methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, n-pentyl, iso-pentyl n-hexyl, 2,2-dimethylbutyl, n-octyl; ethenyl (vinyl), propenyl (allyl), iso-propenyl, n-pentyl, butenyl, isoprenyl or hexa-2-enyl; ethinyl, propinyl or butinyl groups. Any alkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The terms alkenyl and alkynyl refer to an unsaturated straight or branched chain alkyl group (having one, two or more double and/or triple bonds, an alkenyl preferably having one or two double bonds and an alkynyl preferably having one or two triple bonds), containing from two to ten, preferably two to six carbon atoms for example: ethenyl (vinyl), propenyl (allyl), iso-propenyl, n-pentenyl, butenyl, isoprenyl or hexa-2-enyl; ethynyl, propynyl or butynyl groups. Any alkenyl or alkynyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The term heteroalkyl refers to an alkyl, alkenyl or alkynyl group as defined herein where one or more carbon atoms are replaced by an oxygen, nitrogen, phosphorous or sulphur atom for example an alkoxy group such as methoxy, ethoxy, propoxy, iso-propoxy, butoxy or tert.-butoxy, an alkoxyalkyl group such as methoxymethyl, ethoxymethyl, 1-methoxyethyl, 1-ethoxyethyl, 2-methoxyethyl or 2-

ethoxyethyl, an alkylamino group such as methylamino, ethylamino, propylamino, isopropylamino, dimethylamino or diethylamino, an alkylthio group such as methylthio, ethylthio or isopropylthio or a cyano group. It may also refer to one of the above groups containing a keto group. The term heteroalkyl furthermore refers to a group derived from a carboxylic acid or carboxylic acid amide such as acetyl, propionyl, acetyloxy, propionyloxy, acetylamino or propionylamino, a carboxyalkyl group such as carboxymethyl, carboxyethyl or carboxypropyl, a carboxyalkyl ester, an alkylthiocarboxyamino group, an alkoxyimino group, an alkylaminothiocarboxyamino group or an alkoxycarbonylamino group. Any heteroalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, NH_2, OH, SH or NO_2.

The term cycloalkyl refers to a saturated or partially unsaturated (having one, two or more double and/or triple bonds), cyclic group with one, two or more rings, having three to 14 carbon ring-atoms, preferably from five or six to ten carbon ring-atoms, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetralin, cyclopentenyl or cyclohex-2-enyl groups. Any cycloalkyl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH_2, SH, N_3, NO_2, alkyl groups such as methyl or ethyl, heteroalkyl groups such as methoxy, methylamino, dimethylamino or cyanide.

The term heterocycloalkyl refers to a cycloalkyl group as defined herein where one, two or more carbon ring-atoms are replaced by one, two or more oxygen, nitrogen, phosphorous or sulphur atoms or $S(0)_{1-2}$ groups for example piperidino, morpholino or piperazino groups.

The term aryl refers to an aromatic cyclic group with one, two or more rings, having five to 14 carbon ring-atoms preferably from five or six to ten carbon ring-atoms, for example phenyl or naphthyl groups. Any aryl group as defined herein may be substituted with one, two or more substituents, for example F, Cl, Br, I, OH, NH_2, SH, N_3, NO_2, alkyl groups such as methyl or ethyl, heteroalkyl groups such as methoxy, methylamino, dimethylamino or cyanide.

The term heteroaryl refers to an aryl group as defined herein where one, two or more ring-carbon atoms are replaced by an oxygen, nitrogen, boron, phosphorous or sulphur atom, for example pyridyl, imidazolyl, pyrazolyl, quinolinyl, isoquinolinyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, oxadiazolyl, thiadiazolyl, indolyl, indazolyl, tetrazolyl, pyrazinyl, pyrimidinyl and pyridazinyl groups.

The terms arylalkyl, alkylaryl and heteroarylalkyl, heteroalkylaryl refer to groups that comprise both aryl or, respectively, heteroaryl as well as alkyl and/or heteroalkyl and/or cycloalkyl and/or heterocycloalkyl groups.

Preferred and/or advantageous embodiments of the invention are subject-matter of the subclaims.

Preferred are compounds of Formula (I), wherein R^1 is H.

Further preferred are compounds of Formula (I), wherein R^2 is F or H.

Moreover preferred are compounds of Formula (I), wherein R^3 is an ethyl, a 2-propyl, a C3-C6 cycloalkyl, a phenyl or a pyridyl group. All these groups may be

substituted by one, two or more fluorine atoms or amino groups.

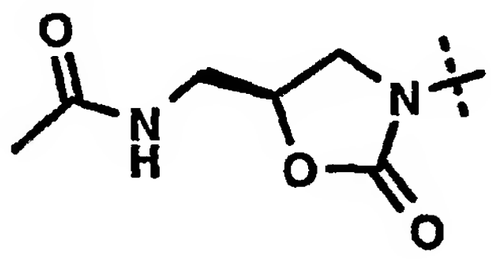
Moreover preferred are compounds of Formula (I), wherein R^3 is a cyclopropyl group.

Further preferred are compounds of Formula (I), wherein R^3 and R^7 together form a bridge of the formula $-O-CH_2-N(Me)-$ or $-O-CH_2-CH(Me)-$. Herein, the preferred stereochemistry at the chiral center is the one giving the S configuration in the final compound.

Moreover preferred are compounds of formula (I), wherein R^4 is hydrogen or a group of formula PO_3H_2, SO_3H, SO_3R^{10}, $PO_3R^9{}_2$, $CH_2OPO_3H_2$ or $COCH_2CH_2COOH$ wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl, and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl or together with the oxygen to which it is bound forms an ester of a naturally occurring amino acid or a derivative thereof (e.g. dimethyl aminoglycine).

Further preferred are compounds of Formula (I), wherein R^8 is a group of the formula $-CH_2NHCOCH=CHAryl$, $-CH_2OHeteroaryl$ (especially -oxa-3-oxazol), $-CH_2NHSO_2Me$, $-CH_2NHCOOMe$, $-CH_2NHCS_2Me$, $-CH_2NHCSNH_2$, $-CH_2NHCSOMe$ or $-CH_2NHCOMe$.

Especially preferred are compounds of Formula (I), wherein R^5 has the following structure:



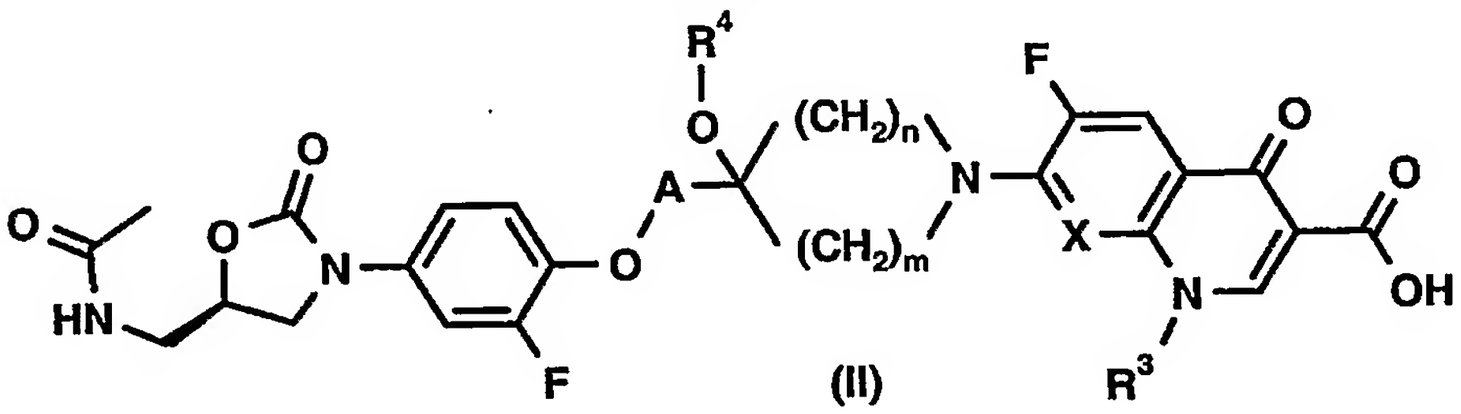
Moreover preferred are compounds of Formula (I), wherein R^7 is H, F, Cl or a methoxy group which may be substituted by one, two or three fluorine atoms.

Further preferred are compounds of formula (I), wherein X is N or CH.

Moreover preferred are compounds of Formula (I), wherein Y is CH.

Further preferred are compounds of Formula (I), wherein A is CH_2 or CH_2CH_2.

Especially preferred are compounds of formula (II)



(II)

wherein A is CH_2 or CH_2CH_2; X is CH, N or C-OMe and R^3 is cyclopropyl or X is CR^7 and R^7 and R^3 together form a bridge of the formula -O-CH_2-CH(Me)-, wherein, the preferred stereochemistry at the chiral center is the one giving the S configuration in the final compound and n, m and R^4 are the same as defined above.

The present invention also relates to pharmacologically acceptable salts, or solvates and hydrates, respectively, and to compositions and formulations of compounds of Formula (I) or (II). The present invention describes procedures to produce pharmaceutically useful agents, which contain these compounds, as well as the use of these compounds for the production of pharmaceutically useful agents.

The pharmaceutical compositions according to the present invention contain at least one compound of Formula (I) or (II) as the active agent and optionally carriers and/or diluents and/or adjuvants. Optionally the pharmaceutical compositions according to the present invention may also contain additional known antibiotics.

Examples of pharmacologically acceptable salts of compounds of Formula (I) or (II) are salts of physiologically acceptable mineral acids like hydrochloric, hydrobromic, sulfuric and phosphoric acid; or salts of organic acids like methanesulfonic, p-toluenesulfonic, lactic, acetic, trifluoroacetic, citric, succinic, fumaric, maleic and salicylic acid. Further examples are alkaline or earth alkaline metal salts, for example sodium, potassium, lithium, calcium or magnesium salts; ammonium salts; or organic base salts, for example methylamine, dimethylamine, trimethylamine, triethylamine, ethylenediamine, ethanolamine, choline hydroxide, meglumin, piperidine, morpholine, tris-(2-hydroxyethyl)amine, lysine or arginine salts. Compounds of Formula (I) or (II) may be solvated, especially hydrated. The hydratisation can occur during the process of production or as a consequence of the hygroscopic nature of the initially water free compounds of Formula (I) or (II). The compounds of Formula (I) or (II) contain asymmetric C-atoms and may be present either as achiral compounds, mixtures of diastereomers, mixtures of enantiomers or as optically pure compounds.

The present invention also relates to pro-drugs which are composed of a compound of Formula (I) or (II) and at least one pharmacologically acceptable protective group which will be cleaved off under physiological conditions,

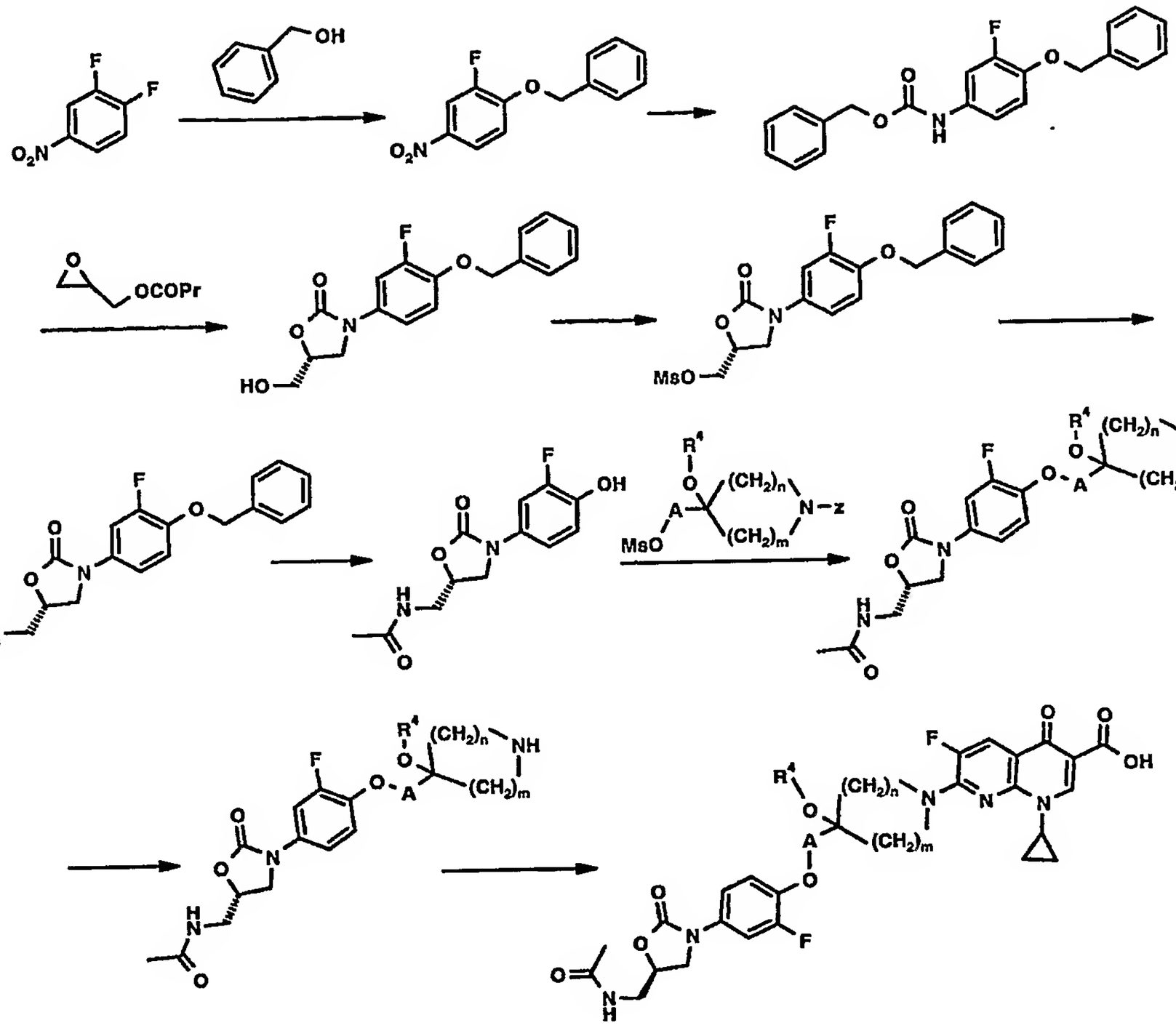
such as an alkoxy-, aralkyloxy-, acyl-, SO_3H, PO_3H_2, acyloxymethyl group (e.g. pivaloyloxymethyl), an 2-alkyl-, 2-aryl- or 2-aralkyl-oxycarbonyl-2-alkylidene ethyl group or an acyloxy group as defined herein, e.g. ethoxy, benzyloxy, acetyl or acetyloxy. Especially preferred are prodrugs of the hydroxy group of a compound of formula (I) or (II) wherein R^4 is H.

As mentioned above, therapeutically useful agents that contain compounds of Formula (I) or (II), their solvates, salts or formulations are also comprised in the scope of the present invention. In general, compounds of Formula (I) or (II) will be administered by using the known and acceptable modes known in the art, either alone or in combination with any other therapeutic agent. Such therapeutically useful agents can be administered by one of the following routes: oral, e.g. as tablets, dragees, coated tablets, pills, semisolids, soft or hard capsules, for example soft and hard gelatine capsules, aqueous or oily solutions, emulsions, suspensions or syrups, parenteral including intravenous, intramuscular and subcutaneous injection, e.g. as an injectable solution or suspension, rectal as suppositories, by inhalation or insufflation, e.g. as a powder formulation, as microcrystals or as a spray (e.g. liquid aerosol), transdermal, for example via an transdermal delivery system (TDS) such as a plaster containg the active ingredient or intranasal. For the production of such tablets, pills, semisolids, coated tablets, dragees and hard, e.g. gelatine, capsules the therapeutically useful product may be mixed with pharmaceutically inert, inorganic or organic excipients as are e.g. lactose, sucrose, glucose, gelatin, malt, silica gel, starch or derivatives thereof, talc, stearinic acid or their salts, dried skim milk, and the like. For the production of soft capsules one may use excipients as are e.g.

vegetable, petroleum, animal or synthetic oils, wax, fat, polyols. For the production of liquid solutions, emulsions or suspensions or syrups one may use as excipients e.g. water, alcohols, aqueous saline, aqueous dextrose, polyols, glycerin, lipids, phospholipids, cyclodextrins, vegetable, petroleum, animal or synthetic oils. Especially preferred are lipids and more preferred are phospholipids (preferred of natural origin; especially preferred with a particle size between 300 to 350 nm) preferred in phosphate buffered saline (pH = 7 to 8, preferred 7.4). For suppositories one may use excipients as are e.g. vegetable, petroleum, animal or synthetic oils, wax, fat and polyols. For aerosol formulations one may use compressed gases suitable for this purpose, as are e.g. oxygen, nitrogen and carbon dioxide. The pharmaceutically useful agents may also contain additives for conservation, stabilisation, e.g. UV stabilizers, emulsifiers, sweetener, aromatisers, salts to change the osmotic pressure, buffers, coating additives and antioxidants.

A daily dosage per patient of about 1mg to about 4000mg especially about 50mg to 3 g is usual with those of ordinary skill in the art appreciating that the dosage will depend also upon the age, conditions of the mammals, and the kind of diseases being treated or prevented. The daily dosage can be administrated in a single dose or can be divided over several doses. An average single dose of about 50mg, 100mg, 250mg, 500mg, 1000mg and 2000mg can be contemplated.

The compounds of formula (I) and (II) can be synthesized according to the following reaction scheme:

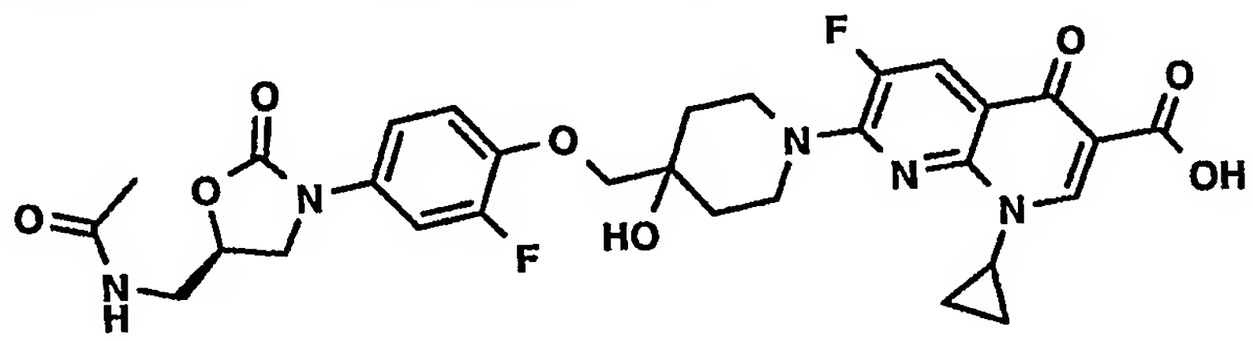


reaction conditions:

step 1: CH_2Cl_2, KOH (50%), 3h, rt; 97%. step 2: H_2, Pt/C, 20h, rt; followed by Z-Cl, acetone/water, $NaHCO_3$, 12h, rt, 98%. step 3: n-BuLi, -60°C, 24h, 80%. step 4: MsCl, triethylamine, CH_2Cl_2; 100%. step 5: NaN_3 in DMF, 90°C, cat. Bu_4NI, 5h, 90%. step 6: H_2, $Pd(OH)_2$, THF, MeOH, 24h, followed by AcOH, Ac_2O, rt, 2h, 70%. step 7: DMF, NaH, 70°C, 12h, 75%. step 8: H_2, $Pd(OH)_2$, MeOH, THF, 24h, RT, 100%. step 9: N-Methylpyrrolidinone, 1-Cyclopropyl-7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthydrin-3-carboxylic acid (commercially available), TMS-Cl, Hünig Base or K_2CO_3, 80°C, 5h, 80%.

Exampl s

Example 1: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Step 1: (4-Benzyloxy-3-fluoro-phenyl)-carbamic acid benzyl ester:

A solution of 34.9g 1-benzyloxy-2-fluoro-4-nitro-benzene (WO03064413) (MW:247.28, 141mmol) and 340mg platine 5% on activated carbon in 350ml ethyl acetate was stirred under hydrogen at rt and normal pressure. The reaction was monitored by HPLC and was complete after twenty hours. The catalyst was filtered over a glas fibre filter, and the filtrate evaporated under reduced pressure to dryness. The oily residue was dissolved in 500ml acetone and treated with 250ml of a saturated solution of sodium bicarbonate and 17.5g of sodium bicarbonate (MW: 84.01, 208mmol). The mixture was cooled to 5°C and treated drop wise with 26.08g of benzyl chloroformate (MW:170.59, 152mmol). The reaction was allowed to stirred at room temperature for two hours and monitored by TLC (hexane/ethyl acetate 3:1). The acetone was evaporated, the residue diluted with 500ml water, and the solid filtered off. The crystals were washed with 500ml water and dried. Yield: 48.05g, 95.8%. MS: 352.5 $(M+H)^+$, 350.8, $(M-H)^-$. Method ESI^+, ESI^-.

Step 2: (5R)-3-(4-benzyloxy-3-fluoro-phenyl)-5-hydroxy-methyl-oxazolidin-2-one:

A stirred solution of 17.5g (4-benzyloxy-3-fluoro-phenyl)-carbamic acid benzyl ester (MW: 351.38, 50mmol) in 30ml of dry tetrahydrofurane was cooled to -78°C with a dry ice/acetone bath. 22.8ml of a 2.3M n-butyl-lithium solution in n-hexane (52.5mmol) was added drop wise and the reaction mixture stirred at - 78 °C for 15 min. 7.92g *R(-)*-glycidyl butyrate (MW: 144.17, 60mmol) were added and the reaction was allowed to warm up to room temperature. The reaction was monitored by HPLC, quenched with a saturated ammonium chloride solution and diluted with 100ml of ethyl acetate. The organic layer was washed with 200ml water and 200ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was crystallized from 200ml of a 1/1-ethyl acetate/hexane mixture. The solid was collected and recrystallized from 150ml of a 9/1 ethyl acetate/dichloro-methane mixture. The colorless crystals were collected and dried. Yield: 10.4-g, 65.5%. MS: 318.1 $(M+H)^+$. Method ESI^+.

Step 3: (5S)-5-azidomethyl-3- (4-benzyloxy-3-fluoro-phenyl)-oxazolidin-2-one:

A solution of 10g (5R)-3-(4-benzyloxy-3-fluoro-phenyl)-5-hydroxymethyl-oxazolidin-2-one (MW: 317.32, 31.51mmol) and 4.78g triethylamine (MW: 101.19, 47.26mmol) in 300ml dichloromethane was treated under stirring at 10°C with 4.32g of methane sulfonyl chloride (MW: 114.55, 37.82mmol). The reaction was stirred at room temperature for one hour and monitored by TLC (ethyl acetate: hexane 1:1). The reaction mixture was quenched with 100ml water and the organic layer washed with 100ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 100ml dimethylformamide, 5.12g sodium azide (MW: 65.01, 78.7mmol) and a catalytic amount of tetrabutyl ammonium

iodide were added. The suspension was stirred at 90 °C over night. The reaction was monitored by HPLC. The dimethylformamide was evaporated under reduced pressure, the residue dissolved in 200ml dichloromethane and the organic layer washed successively with 100ml water and 100ml brine. The dichloromethane solution was dried over magnesium sulfate, filtered, and the filtrate evaporated under reduced pressure. The residue was crystallized from 150ml of a 1/1 mixture of ethyl acetate: hexane. The crystals were collected to afford an off white solid. Yield: 10.4-g, 97%. MS: 343.1 $(M+H)^{+-}$. Method: ESI^{+}.

Step 4: N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide:

A suspension of 10.4g (5S)-5-azidomethyl-3- (4-benzyloxy-3-fluorophenyl)oxazolidin-2-one (MW: 342.33, 30.38mmol) and 1.5g of palladium 10% on activated carbon in 400ml of a 1:1 methanol:ethyl acetate mixture was stirred at room temperature under hydrogen for two days. The catalyst was filtered off using a glass fibre filter paper and the filtrate evaporated under reduced pressure. The residue was dissolved in 100ml of acetic acid, and treated with 3.72g of acetic anhydride (MW: 102.09, 36.45mmol). The solvent was evaporated under reduced pressure and the residue crystallized from a 1:1 ethyl acetate: hexane mixture to afford an off white solid. Yield: 6.76-g, 83%. MS: 269.4 $(M+H)^{+}$, 267.3, $(M-H)^{-}$. Method ESI^{+}, ESI^{-}.

Step 5: 4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid benzylester:

A suspension of 22.72g 1-oxa-6-aza-spiro[2.5]octane-6-carboxylic acid benzyl ester (WO9803507) (MW: 247.29, 92mmol), 21.45g N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-

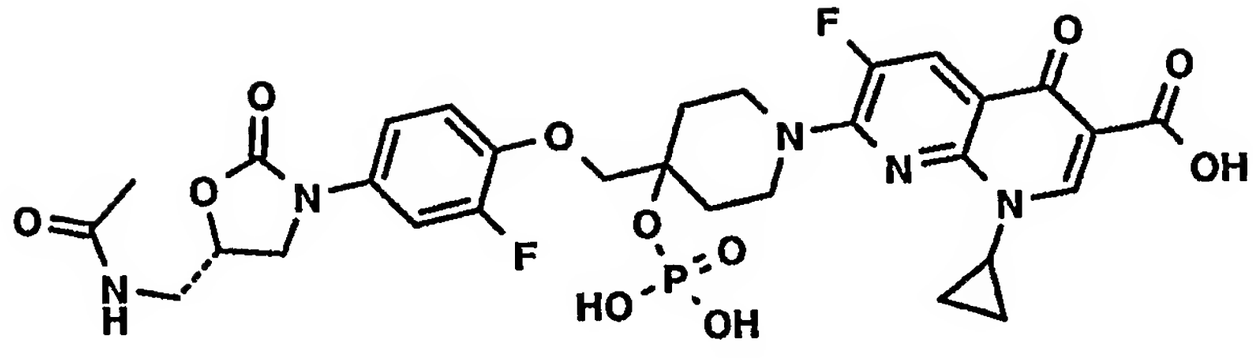
oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 80mmol) and 16.58g potassium carbonate (MW: 138.20, 120mmol) in 150ml dimethylformamide was stirred at 100°C for 7 hours. The reaction was monitored by TLC (dichloromethane / methanol 9:1). The dimethylformamide was evaporated under reduced pressure and the residue was dissolved in 600ml of a 9:1 dichloromethane /methanol mixture. The organic layer was washed with 400ml water and 400ml brine. The organic layer was dried over magnesium sulfate, filtered, and the filtrate diluted with 250ml ethyl acetate. The mixture was concentrated under reduced pressure to a final volume of 400ml. The slurry was stirred at room temperature over night. The crystals were filtered and washed successively with 150ml ethyl acetate and 100ml pentane. Yield: 31.65 g, 76.7%. MS: 516.8 $(M+H)^+$, Method ESI^+.

Step 6: N- [{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-yl-methoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide:
A suspension of 31g 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluorophenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid benzylester (MW: 515,54 60.13mmol) and 2.5 g of palladium 10% on activated carbon in 310ml methanol and 150ml ethyl acetate was stirred under hydrogen for 4 hrs. The reaction was monitored by TLC (ethyl acetate). The reaction slurry was diluted with 300ml methanol, warmed to 40 °C, and the catalyst filtered off using a glass fibre filter paper. The filtrate was concentrated to 150ml, diluted with 300ml ethyl acetate and concentrated again to 200ml. 200ml of diethyl ether were added, and the suspension was cooled to 0°C under stirring. The solid was collected and dried. Yield: 21.6-g, 94.3%. MS: 382.6 $(M+H)^+$, Method ESI^+.

Step7: 7-(4-{[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid:

A suspension of 71mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW: 282.66, 0.25mmol), 95mg N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide (MW: 381.40, 0.25mmol) 102mg triethylamine (MW: 101.19, 1.0mmol) and 81mg trimethylchlorsilan (MW: 108.64, 0.75mmol) in 1ml N-methyl-pyrrolidin-2-one was heated at 80°C under stirring for 5 hours. The reaction was monitored by TLC (dichloromethane: methanol 9:1). The N-methyl-pyrrolidin-2-one was evaporated, the residue dissolved in 20ml of a 9:1 dichloromethane : methanol mixture, and the solution washed sequentially with 10ml of 0.1 N aqueous hydrochloric acid and 20ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated. The residue was dissolved in 10ml of a 9:1 dichloromethane: methanol mixture and diluted with 20ml ethyl acetate. The precipitated solid was collected to afford an off white solid. A second crop is obtained by concentration under reduced pressure of the mother liquor. Yield: 100mg, 64%. MS: 628.8 $(M+H)^+$, 626.8. $(M-H)^-$ Method ESI^+, ESI^-

Example 2: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-phosphonooxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



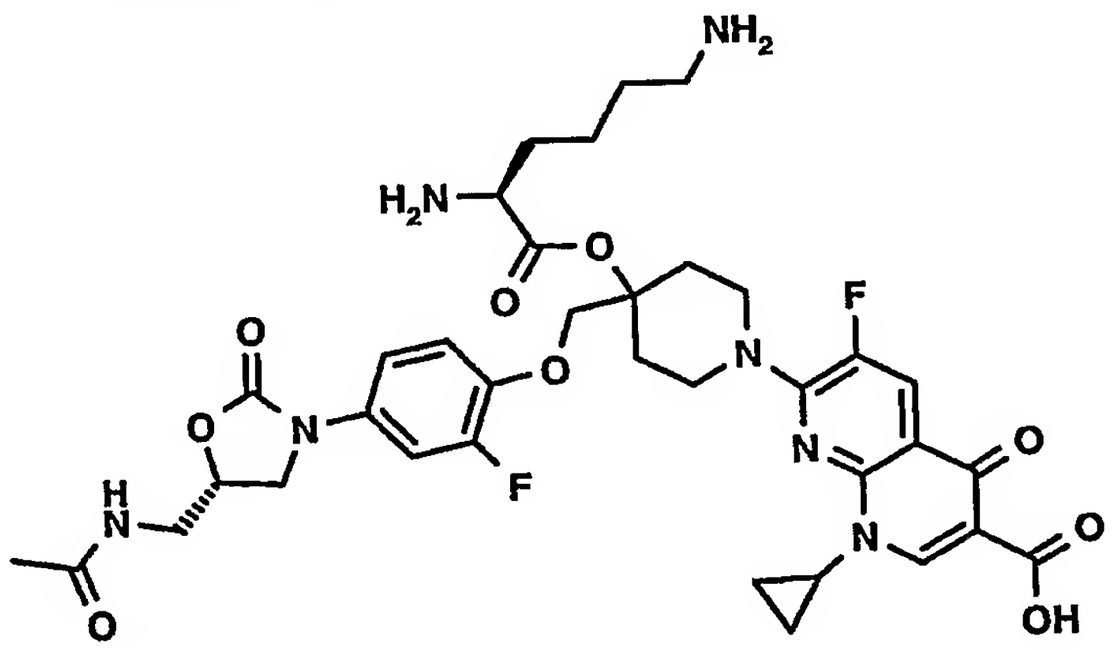
Step 1: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine -3-carboxylic acid:

A suspension of 125mg 7-(4-{[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (MW: 627.60, 0.2mmol) and 42mg tetrazole (MW:70.05, 0.6mmol) in 1ml dichloromethane was treated with 138mg of dibenzyl N,N-diisopropylphosphoramidite (MW: 345.42, 0.4mmol). The original suspension slowly cleared. The solution was stirred at room temperature for two hours and monitored by TLC. (dichloromethane/methanol 9:1). The reaction mixture was cooled to 0°C and treated with a 0.6ml of a 0.5M m-chloroperbenzoic acid solution in dichloromethane. The mixture was stirred for two hours at room temperature and diluted with 20ml dichloromethane. The organic layer was washed successively with 20ml of a saturated aqueous sodium bicarbonate solution and 20ml of brine and dried over magnesium sulfate. The slurry was filtered and the filtrate evaporated under reduced pressure. The residue was purified by chromatography over silica using a 9/1 dichloro-methane/methanol mixture as eluent to afford an off white solid. Yield: 158mg, 89%.MS: 889.3 $(M+H)^+$, 887.0 $(M-H)^-$ Method ESI^+, ESI^-.

Step 2: 7-(4-{4-[(5S)-(5-Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-phosphonooxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine -3-carboxylic acid:

A suspension of 158mg 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine -3-carboxylic acid (MW: 887.84, 0.177mmol) and 20mg of palladium hydroxide 20% on activated carbon in 20ml of a 6/3/1 dichloromethane/methanol/ water mixture was stirred at room temperature under hydrogen for three hours. The catalyst was filtered off using a glass fibre filter paper. The solvents were evaporated under reduced pressure and the residue dissolved in 10ml methanol. The solution was diluted with 20ml water while a white solid precipitated. The solid was collected and dried. Yield: 85mg, 68%. MS: 709.0 $(M+H)^+$, 706.5 $(M-H)^-$ Method ESI^+, ESI^-.

Example 3: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-diamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Step 1: 4-{4-[(5S)-(5-Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester:

In analogy of example 1 step 5 by reacting 3.83g 1-oxa-6-aza-spiro[2.5]octane-6-carboxylic acid tert-butyl ester (WO0204462) (MW: 213.28 18mmol), 4.02g N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 15mmol) and 3.1g potassium carbonate (MW: 138.20, 22.5mmol) in 30ml dimethylformamide. Yield: 4.89-g, 67%. MS: 482.6 $(M+H)^+$, Method ESI^+.

Step 2: 4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidine-1-carboxylic acid tert-butyl ester:

A suspension of 96mg of 4-{4-[5-(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (MW: 481.52, 0.2mmol), 195mg of Z-Lys (Z)-OH (MW: 414.46, 0.4mmol) and 49mg of 4-dimethylaminopyridine (MW: 122.17, 0.4mmol) in 2ml dichloromethane was treated under stirring at room temperature with 115mg N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimid hydrochloride (MW: 191.70, 0.6mmol). The reaction mixture was stirred over night. The mixture was diluted with 20ml ethyl acetate and the organic layer washed successively with 10ml 1 N aqueous hydrochloric acid, 20ml water and 20ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated to dryness. The residue was purified by chromatography on silica, using a 9/1 dichloromethane/ methanol mixture as eluent to leave a colorless sticky oil. Yield: 150mg, 88%. MS: 878.8 $(M+H)^+$, Method ESI^+.

Step 3: 2,6-Bis-benzyloxycarbonylamino-hexanoic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester hydrochloride:

200mg of 4-{4-[5-(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidine-1-carboxylic acid tert-butyl ester (MW: 977.97, 0.22mmol) were dissolved in 4ml of a 1.25M dry hydrochloric acid in methanol. The reaction was stirred at 40°C for two hours, and the solvent removed by distillation under reduced pressure to leave a off white solid. Yield: 178mg, quantitative. MS: 778.8 $(M+H)^+$, Method ESI^+.

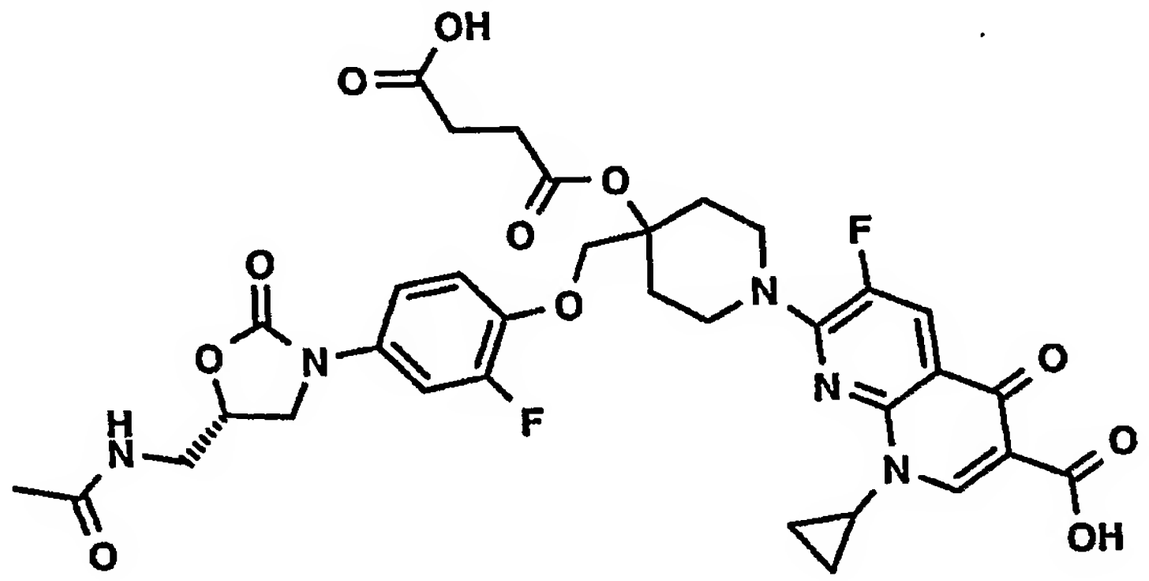
Step 4: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

In analogy to example 1 step 7, with 62mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW:282.66, 0.25mmol), 178mg 2,6-bis-benzyl-oxycarbonylamino-hexanoic acid 4-{4-[5-(5S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester hydrochloride (MW: 814.31, 0.22mmol), 90mg triethylamine (MW: 101.19, 0.88mmol) and 48mg trimethylchlorsilan (MW: 108.64, 0.44mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 94mg, 42%. MS: 1025.3 $(M+H)^+$, Method ESI^+.

Step 5: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-diamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

A suspension of 94mg 7-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(2,6-bis-benzyloxycarbonylamino-hexanoyloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid (MW: 1024.05, 0.091mmol) and 20mg of palladium hydroxide 20% on activated carbon in 20ml of a 6/3/1 dichloromethane/methanol/water mixture was stirred at room temperature under hydrogen for four hours. The catalyst was filtered off using a glass fibre filter paper. The solvents were evaporated under reduced pressure and the residue dissolved in 10ml methanol. The solution was diluted with 20ml water while a white solid precipitated. The solid was collected and dried. Yield: 29mg, 43%. MS: 757.0 $(M+H)^+$, 755.2 Method ESI^+, ESI^-.

Example 4: Succinic acid mono-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl] ester



Step 1: Succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-tert-butoxy-carbonyl-piperidin-4-yl ester benzyl ester:

In analogy of example 3 step 2 with 825mg 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidine-1-carboxylic acid tert-

butyl ester (MW: 481.52, 1.71mmol), 1.07g of succinic acid monobenzyl ester (MW: 208.21, 5.14mmol) and 0.63g of 4-dimethylaminopyridine (MW: 122.17, 5.1mmol) in 10ml dichloromethane was treated under stirring at room temperature with 1.3g N-(3-dimethylaminopropyl)-N´-ethyl-carbodiimid HCl (MW: 191.70, 6.8mmol). Yield: 820mg, 70%. MS: 673.3 $(M+H)^+$, Method ESI^+.

Step 2: Succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-piperidin-4-yl ester benzyl ester:

820mg of succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-tert-butoxy-carbonyl-piperidin-4-yl ester benzyl ester (MW: 671.72, 1.23mmol) were dissolved in 4ml of trifluoro acetic acid. The reaction mixture was stirred at room temperature for one hour. The solvent was evaporated, the residue dissolved in 30ml of a 9/1 dichloromethane/methanol mixture and the organic layer washed successively with 30ml of a saturated aqueous sodium bicarbonate solution and 30ml of brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was purified by chromatography over silica, using a 95/5 dichloromethane/ methanol mixture with 2% triethylamine as eluent. Yield: 420mg, 60%. MS: 572.7 $(M+H)^+$, Method ESI^+.

Step 3: Succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl ester benzyl ester:

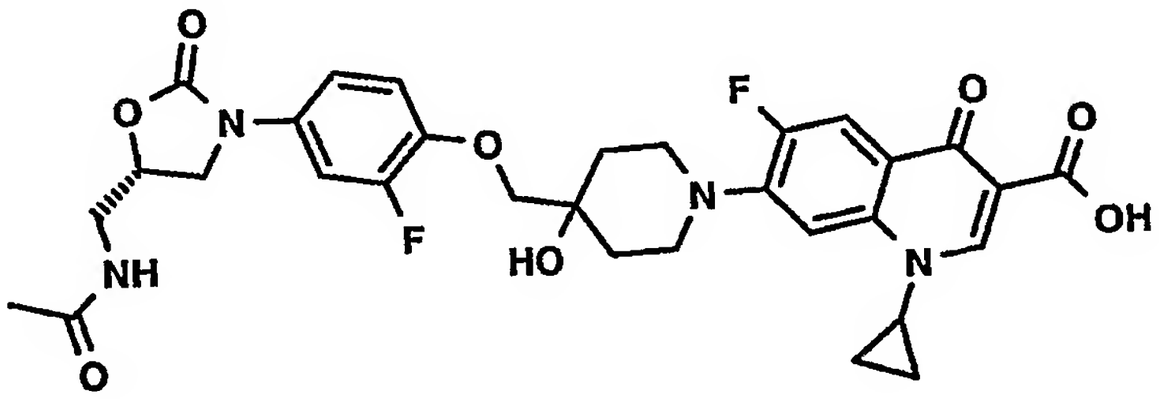
In analogy to example 1 step 7, with 113mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW:282.66, 0.4mmol), 230mg succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-

fluoro-phenoxymethyl}-piperidin-4-yl ester benzyl ester (MW: 571.60, 0.4mmol), 161mg triethylamine (MW: 101.19, 1.6mmol) and 87mg trimethylchlorsilan (MW: 108.64, 0.8mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 25mg, 7.6%. MS: 819 $(M+H)^+$, 817.8, Method ESI^+, ESI^-.

Step 4: Succinic acid mono-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl] ester:

In analogy to example 3 step 5 with 22mg succinic acid 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-1-(6-carboxy-8-cyclopropyl-3-fluoro-5-oxo-5,8-dihydro-[1,8]naphthyridin-2-yl)-piperidin-4-yl ester benzyl ester (MW: 817.80, 0.026mmol) and 2mg of palladium hydroxide 20% on activated carbon in 20ml of a 1/1 tetrahydrofuran/ methanol mixture. Yield: 16mg, 81%. MS: 729 $(M+H)^+$, 727 $(M+H)^-$, Method ESI^+, ESI^-.

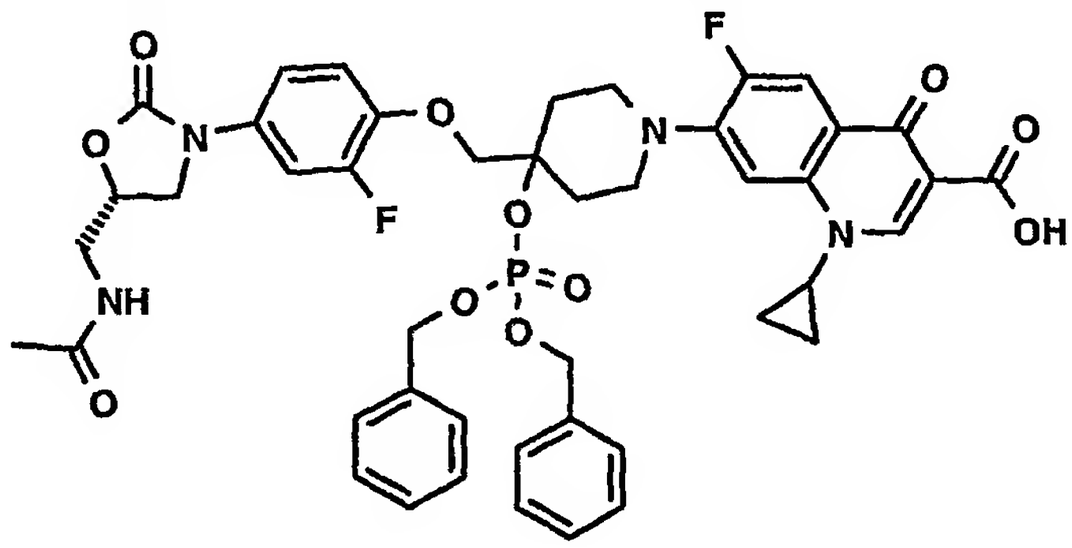
Example 5: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



A solution of 60g N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide. ($C_{18}H_{24}FN_3O_5$, MW: 381.40 0.157 mole) and 26.87ml of ethyl diisopropylamine (MW: 129.25, 0.157 mole)

in 300ml N-methyl-pyrrolidin-2-one was treated with 67.81g (7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid-boron diacetate complex (MW:410.57, 0.165 mole) and the mixture was stirred at 80°C for 5 hours. The N-methyl-pyrrolidin-2-one was evaporated under reduced pressure and residue was dissolved in 300ml of methanol. Anhydrous hydrogen chloride was bubbled through the solution at 10 °C for 30 minutes. The solution was stirred at room temperature while a yellow solid precipitated. The conversion of the boron complex to the free acid was monitored by HPLC. The mixture was diluted with 300ml ethyl acetate. The solid was filtered and washed with 100ml of 8/2 ethyl acetate/methanol and 100ml of ethyl acetate. The yellow solid was dried to leave 86.4 g of a yellow solid. The solid was dissolved in 200ml dimethylsulfoxyde at 40 °C, and the yellow solution was added under stirring to 1000ml water. The yellow solid was collected, washed with water and dried. Yield: 73g, 74.5%. MS: 627.8 $(M+H)^+$, 625.8 $(M+H)^-$, Method ESI^+, ESI^-.

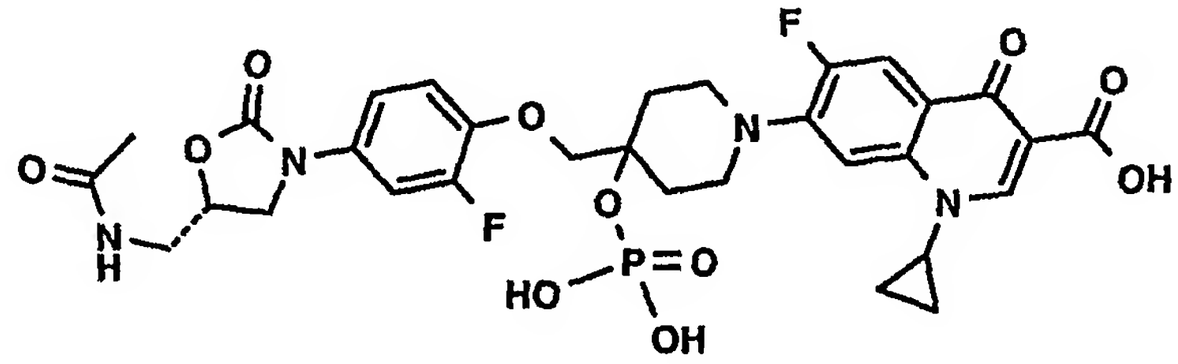
Example 6: 7-[4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



A suspension of 35g 7-(4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (MW: 626.61, 55.85mmol) and 6,45g tetrazole (MW: 70.05, 92.15mmol) in 700ml dichloromethane was treated at room temperature under stirring with a solution of 31.8g dibenzyldiisopropylphosphoramidit (MW: 345.42, 92.15mmol) in 20ml dichloromethane. The reaction was monitored by TLC (dichloromethane/methanol 9:1). The reaction was stirred for one hour and the mixture was washed at 0°C with 200ml 1N aqueous hydrochloric acid and 100ml of a saturated sodium bicarbonate solution. The water layer were backwashed with 200ml dichloromethane. The combined organic layer were concentrated to 500ml and treated at roomtemperature with 13,2ml of a 70 % ter-butyl hydroperoxid solution in water (MW:90.12, 95mmol). The reaction was stirred for 30 min, diluted with 500ml dichloromethane and the organic layer washed with 200ml 1N aqueous hydrochloric acid and with 300ml brine. The organic layer was dried over magnesium sulfate, filtered and the filtrate evaporated under reduced pressure. The residue was dissolved in 400ml dichloromethane and diluted with 400ml N-hexane. The mixture was concentrated (300-mbar, 40°C bath temperature) to a volume of 400ml. The sticky oil was decanted and dissolved in 400ml of refluxing methanol. The solution was concentrated to 300ml under reduced pressure and stirred over night at RT. The slurry was cooled to 0°C and the solid collected. Yield: 27.60g, 55.6%. MS: 888.3 $(M+H)^+$, 885.8 $(M+H)^-$, Method ESI^+, ESI^-.

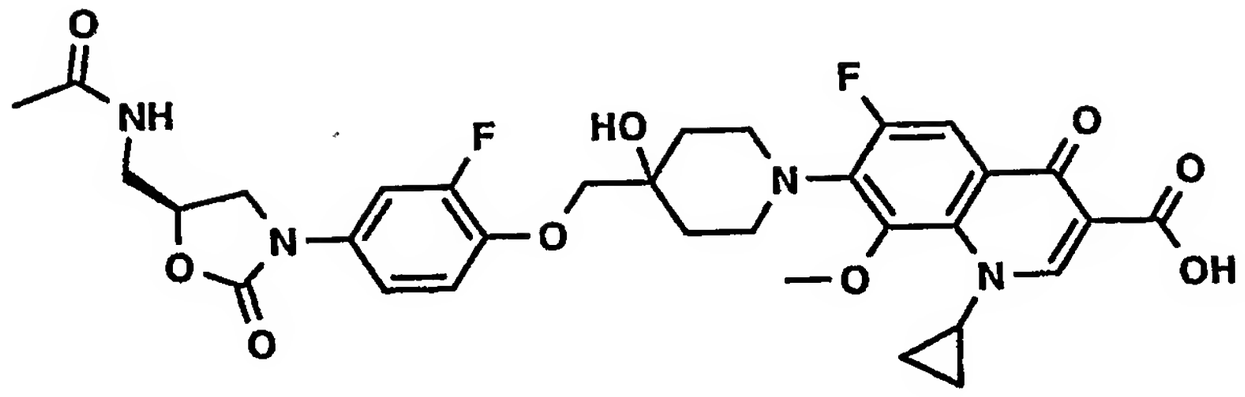
Example 7: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-phosphonooxy-

piperidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



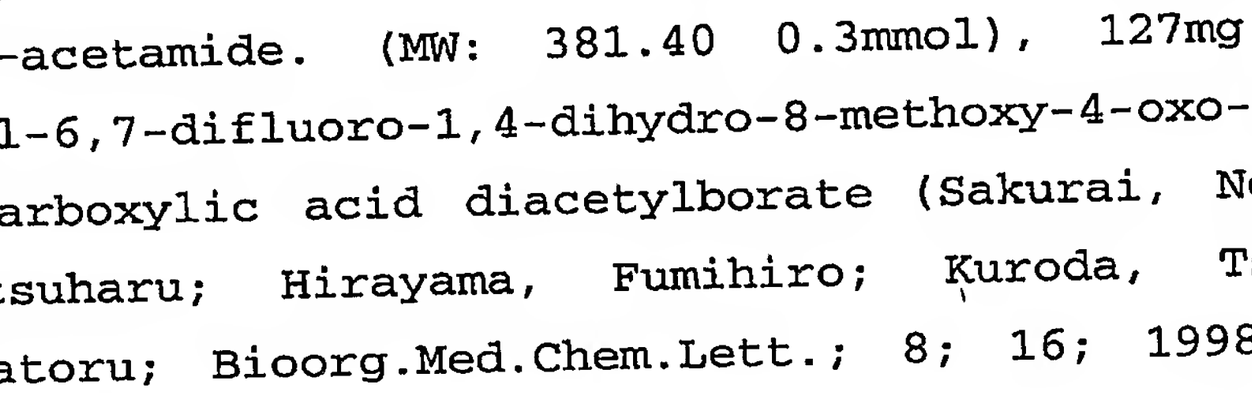
27g 7-[4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-(bis-benzyloxy-phosphoryloxy)-piperidin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (MW: 886.85, 30.44mmol) were suspended in 600ml acetonitrile and treated with 53ml of a 33% solution of anhydrous hydrobromic acid in acetic acid. The yellow suspension was diluted with 150ml of acetic acid and was heated to 45°C. The reaction was monitored by HPLC/MS and was complete after 3 hours. The sticky suspension was added to 1.5 L of water under stirring. The off white crystals were collected, washed with 300ml water, 150ml ethanol and 150ml ether. The solid was suspended in 1.3L water and treated with 35ml (35mmol) of a 1M aqueous sodium hydroxide solution. The solid dissolved, and the brown-yellow solution was treated with 15 g of activated charcoal and filtered. The filtrate was extracted with 3 portions of 200ml of a 95/5 dichloromethane/ methanol mixture. The water layer was treated with 40ml of 1 M HCl solution and the product crystallized by stirring. The solid was collected and dried. Yield: 17.3-g, 80.4 %. MS: 609.7 $(M+H)^+$, 607.8 $(M+H)^-$, Method ESI^+, ESI^-.

<u>Example 8:</u> 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 5 with 114mg N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}]-acetamide. (MW: 381.40 0.3mmol), 127mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid diacetylborate (Sakurai, Nobuhiro; Sano, Mitsuharu; Hirayama, Fumihiro; Kuroda, Tsuyoshi; Uemori, Satoru; Bioorg.Med.Chem.Lett.; 8; 16; 1998; 2185-2190) (MW: 423.137, 0.3mmol) and 38mg of ethyl diisopropylamine (MW: 129.25, 0.3mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 137mg, 69.5 %. MS: 658.2 $(M+H)^+$, 655.8 $(M+H)^-$, Method ESI^+, ESI^-.

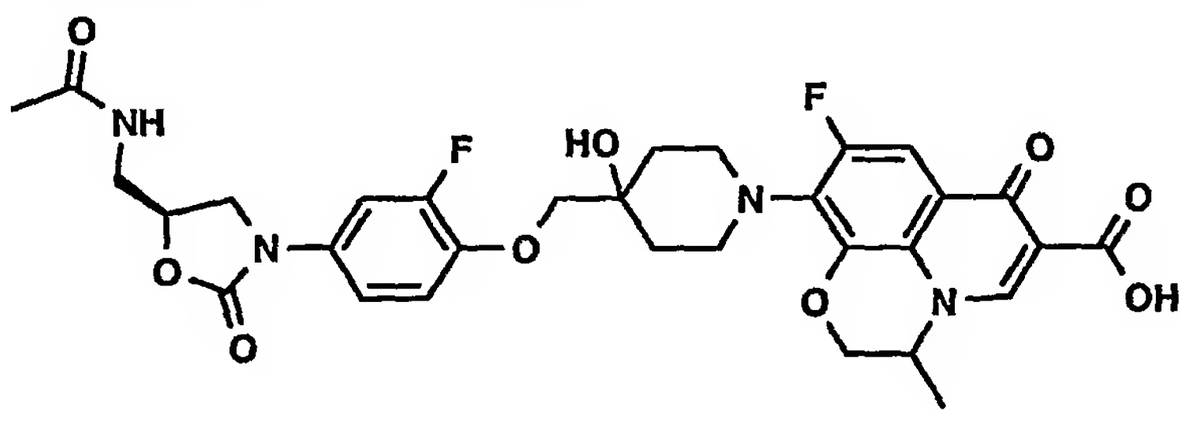
Example 9: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 5 with 114mg N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}]-acetamide. (MW: 381.40 0.3mmol), 121mg of 1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-

carboxylatoboron diacetate (WO03032962) (MW: 405.15, 0.3mmol) and 77mg of ethyl diisopropylamine (MW: 129.25, 0.6mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 117mg, 61.2 %. MS: 639.8 $(M+H)^+$, 637.5 $(M+H)^-$, Method ESI^+, ESI^-.

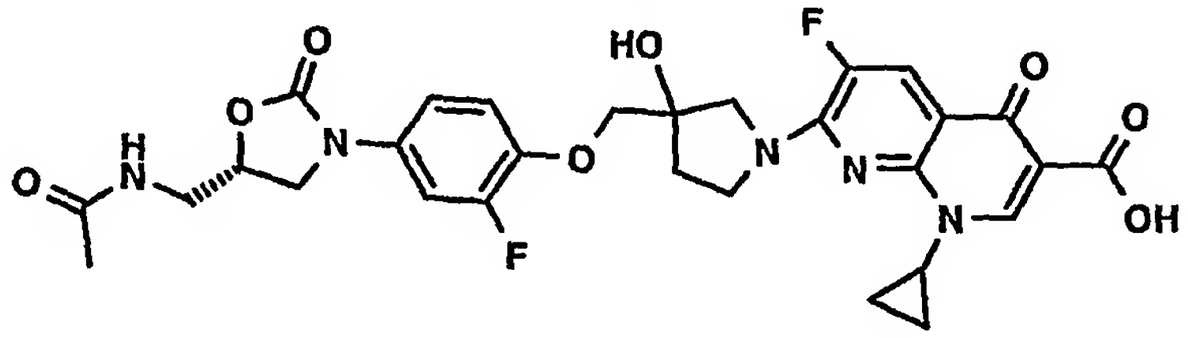
Example 10: 9-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-piperidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



A solution of 140mg of 9-10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxilic acid (MW: 281.22, 0.5mmol), 191mg of N-[{(5S)-3[3-fluoro-4-(4-hydroxy-piperidin-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}]-acetamide (MW: 381.40, 0.5mmol), and 129mg of ethyl diisopropylamine (MW: 129.25, 1mmol) was stirred at 80°C in 1ml of N-methyl-pyrrolidin-2-one for 24 hours. The solvent was evaporated under reduced pressure. The residue was dissolved in methanol and treated with 10ml of a 1.2 M anhydrous hydrogen chloride solution in methanol. The methanol was evaporated and the residue digested in ethyl acetate. The solid was collected and crystallized twice from a dichloromethane/ethanol mixture. Yield: 88mg, 27 %. MS: 643.7 $(M+H)^+$, 641.5 $(M+H)^-$, Method ESI^+, ESI^-.

Example 11: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-

pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Step 1: 1-Oxa-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester:

A solution 3-methylen-pyrrolidine-1-carboxylic acid benzyl ester (WO9624593) in 5ml of dichloromethane was treated with 2.16g sodium bicarbonate (MW: 84.01 26.28mmol) and 2.47g of 80% m-chlor-perbenzoic acid (MW: 172.57, 11.48mmol).The reaction mixture was stirred at room temperature for three hours. The reaction mixture was diluted with 20ml of a saturated aqueous sodium sulfite solution and 45ml of dichloromethane. The organic layer was successively washed with 30ml of an aqueous saturated sodium bicarbonate solution and brine. The organic layer was dried over magnesium sulfate. The residue was purified by chromatography on silica (1/1 ethyl acetate/n-hexane) to afford a off white solid. Yield: 440mg, 57 %. MS: 234.1$(M+H)^+$, Method ESI^+.

Step 2: 3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidine-1-carboxylic acid benzyl ester:

A solution of 420mg of N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 1.56mmol) in 2ml dimethylformamide was treated with 83mg sodium hydride. The suspension was stirred for one hour at room temperature. A solution of 440mg 1-oxa-5-aza-spiro[2.4]heptane-5-carboxylic acid benzyl ester (MW:

233.26, 1.88mmol) in 1ml DMF was added and the mixture was stirred at 70°C for three hours. The dimethylformamide was evaporated under reduced pressure and the residue was purified by chromatography over silica (95/5 dichloromethane/methanol mixture with 1% ammonia) to afford an off white powder. Yield: 630mg, 80 %. MS: 502.5 $(M+H)^+$, Method ESI^+.

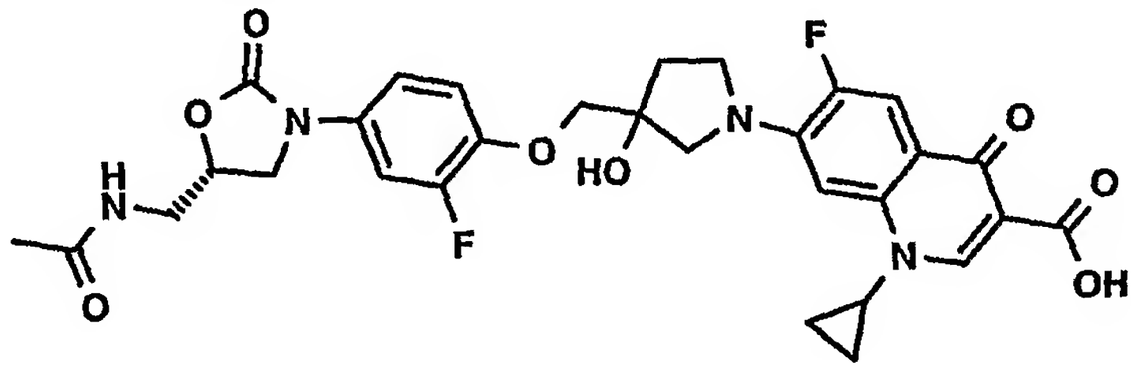
Step 3: N-{(5S)-3-[3-Fluoro-4-(3-hydroxy-pyrrolidin-3-yl-methoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide:

A suspension of 660mg 3-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidine-1-carboxylic acid benzyl ester (MW: 501.51, 1.31mmol) and 20mg palladium 10% on activated carbon in 20ml of a 1/1 ethyl acetate / methanol mixture was stirred for twelve hours under hydrogen. The catalyst was filtered on a glass fiber filter paper and the filtrate evaporated under reduced pressure to afford a colorless oil. Yield: 400mg, 83.2 %. MS: 368.4 $(M+H)^+$, Method ESI^+.

Step 4: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid:

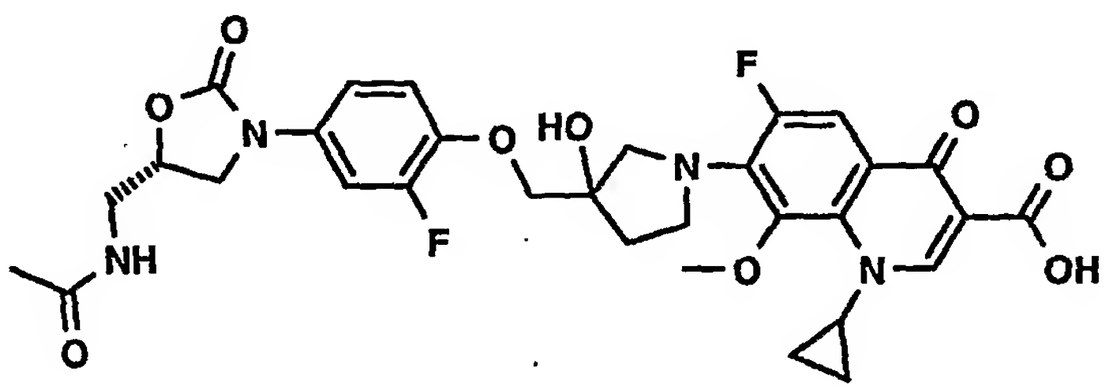
In analogy to example 1, step 7 with 39mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW: 282.66, 0.24mmol), 99mg N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide. (MW: 367.38, 0.24mmol) 101mg triethylamine (MW: 101.19, 1.0mmol) and 80mg trimethylchlorsilan (MW: 108.64, 0.75mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 70mg, 46 %. MS: 614.7$(M+H)^+$, 612.7 $(M+H)^-$, Method ESI^+, ESI^-.

Example 12: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 5 with 106mg N-{(5S)-3-[3-fluoro-4-(3-hydroxypyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide. (MW: 367.38, 0.29mmol) 119mg (7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid-boron diacetate complex (MW:410.57, 0.29mmol) and 75mg of ethyl diisopropylamine (MW: 129.25, 0.58mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 19mg, 11 %.MS: 613.5 $(M+H)^+$, 611.5 $(M+H)^-$, Method ESI^+, ESI^-.

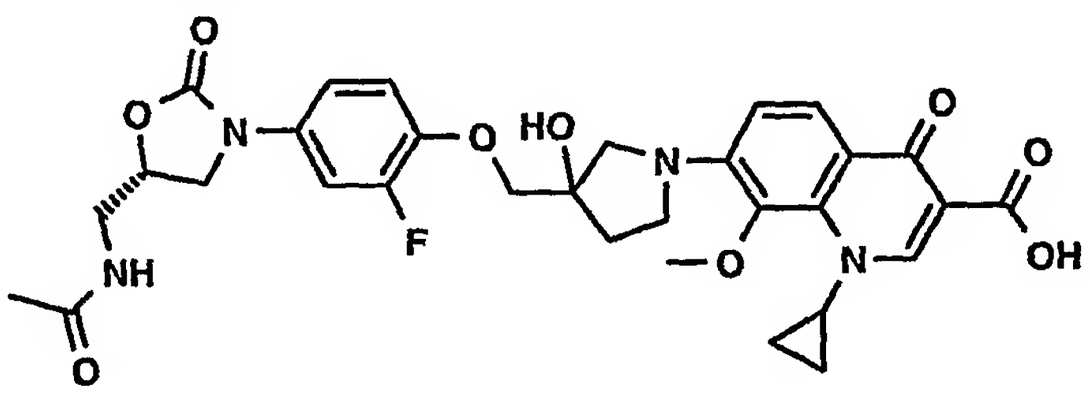
Example 13: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-6-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



In analogy to example 5 with 143mg N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 367.38, 0.39mmol), 165mg of 1-cyclopropyl-6,7-difluoro-1,4-dihydro-8-methoxy-4-oxo-3-

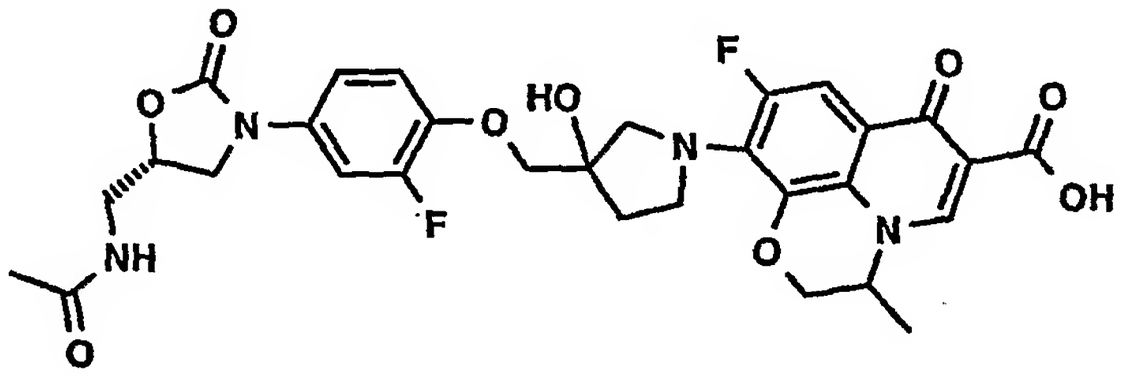
quinolinecarboxylic acid diacetylborate (MW: 423.137, 0.39mmol) and 100mg of ethyl diisopropylamine (MW: 129.25, 0.78mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 143mg, 57 %. MS: 643.7 $(M+H)^+$, 641.7 $(M+H)^-$, Method ESI^+, ESI^-.

Example 14: 7-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



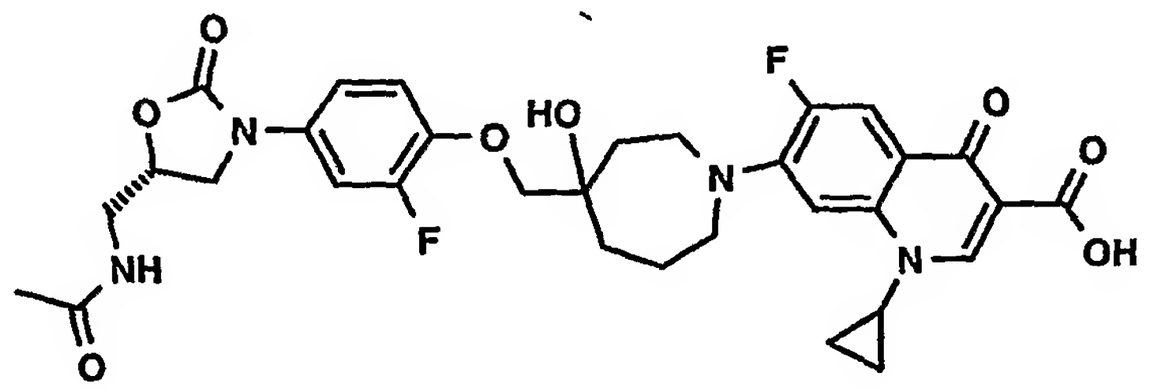
In analogy to example 5 with 48mg N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 367.38, 0.13mmol), 53mg of 1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylatoboron diacetate (MW: 405.15, 0.13mmol) and 33mg of ethyl diisopropylamine (MW: 129.25, 0.26mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 41mg, 50 %. MS: 625.8 $(M+H)^+$, 623.8 $(M+H)^-$, Method ESI^+, ESI^-.

Example 15: 9-(3-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-3-hydroxy-pyrrolidin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



In analogy to example 10 with 110mg of 9-10-difluoro-2,3-dihydro-3-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxilic acid (MW: 281.22, 0.39mmol), 143mg of N-{(5S)-3-[3-fluoro-4-(3-hydroxy-pyrrolidin-3-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide. (MW: 367.38, 0.39mmol), and 100mg of ethyl diisopropylamine (MW: 129.25, 0.78mmol) in 2ml of N-methyl-pyrrolidin-2-one. Yield: 103mg, 42 %.MS: 629.8 $(M+H)^+$, Method ESI^+.

Example 16: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



Step 1: 4-Methylene-azepane-1-carboxylic acid tert-butyl ester:

A solution of 1g methyltriphenylphosphoniumbromide (MW: 357.22, 2.79mmol) in 20ml of tetrahydrofurane was treated at -78°C with 1.22ml of a 2.3 M n-butyl lithium solution in N-hexane (2.8mmol). The reaction mixture was stirred at -78°C for ten minutes, then at 0°C for one hour. The yellow suspension was cooled to -78°C and treated with a solution of 595mg 4-oxo-azepane-1-carboxylic acid tert-butyl ester (WO 2000044376) (MW: 213.279, 2.78mmol) in 10ml tetrahydrofurane. The reaction mixture was stirred at room temperature for one and half hour. The reaction mixture was quenched with 30ml of a saturated aqueous solution of

ammonium chloride, diluted with 30ml of ethyl acetate. The organic layer was successively washed with 30ml water and 30ml brine, dried over magnesium sulfate and filtered. The filtrate was evaporated under reduced pressure and the residue purified by chromatography over silica. (cyclohexane:ethyl acetate 1:1). Yield: 487mg, 83%. NMR ($CDCl_3$): 1.35 ppm (s, 9 H, tert-but.); 1.6 ppm (m, 2H, $-CH_2-$), 2.14 ppm (m, 2H), 2.33 ppm (m, 2H); 3.29 ppm (m, 4H, $N-CH_2$); 4.67 ppm (m, 2H, vinyl-CH_2).

Step 2: 1-Oxa-6-aza-spiro[2.6]nonane-6-carboxylic acid tert-butyl ester:

In analogy to example 11 step 1 with 4-methylene-azepane-1-carboxylic acid tert-butyl ester (MW:211.307, 1.73mmol), 1.16g sodium bicarbonate (MW: 84.01 13.8mmol) and 1.36g of 80% m-chloroperbenzoic acid (MW172.57, 6.05mmol) in 5ml of dichloromethane. Yield: 250mg, 63 %. MS: 228.8 $(M+H)^+$, 127.8 $(M-(CH_3)_3COCO)$ method ESI^+.

Step 3: 4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepane-1-carboxylic acid tert-butyl ester:

In analogy to example 1 step 5 with 247mg of 1-oxa-6-aza-spiro[2.6]nonane-6-carboxylic acid tert-butyl ester. (MW: 227.31 1.08mmol), 296mg N-[(5S)-{3-(3-fluoro-4-hydroxy-phenyl)}-2-oxo-oxazolidin-5-ylmethyl]-acetamide (MW: 268.246, 80mmol) and 228mg potassium carbonate (MW: 138.20, 1.65mmol) in 150ml dimethylformamide. Yield: 334mg, 62 %. MS: 496.8 $(M+H)^+$, 440.8 $(M-C(CH_3)_3+H)^+$, Method ESI^+.

Step 4: N-{(5S)-3-[3-Fluoro-4-(4-hydroxy-azepan-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide:

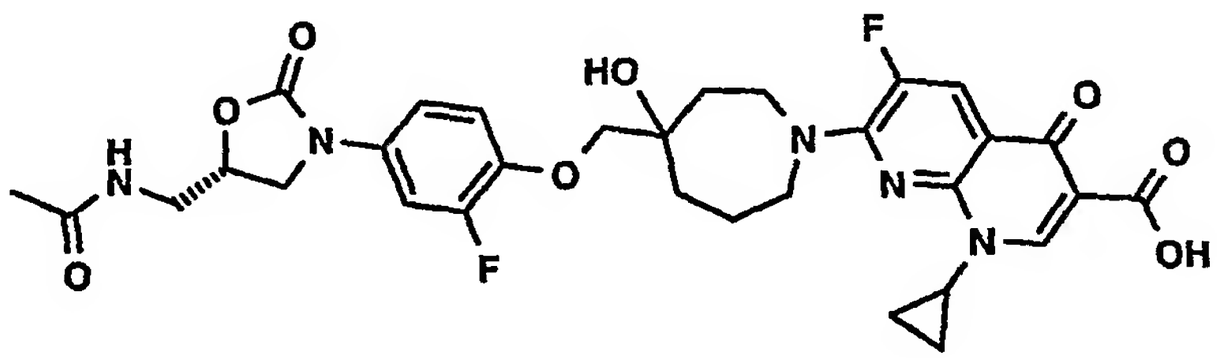
A solution of 334mg 4-{4-[(5S)-5-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepane-

1-carboxylic acid tert-butyl ester (MW:495.55, 0.674mmol) in 3ml of a 1.25 M anhydrous hydrogen chloride solution in methanol was stired at 35°C for four hours. The solvent was evaporated under reduced pressure. The residue was dissolved in 4ml water and the water layer neutralized to pH 7 with a saturated sodium bicarbonate solution. The water was evaporated and the residue dissolved in 30ml of a 9/1 dichloromethane/methanol mixture. The unsoluble salt were filtered and the filtrate evaporated to dryness to afford off white solid. Yield 266mg, quant. MS: 395.8 $(M+H)^+$, 440.6 $(M+HCOO^-)$, Method ESI^+, ESI^-.

Step 5: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid:

In analogy to example 5 with 150mg N-{(5S)-3-[3-fluoro-4-(4-hydroxy-azepan-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-yl-methyl}-acetamide (MW: 395.43) and 98mg of ethyl diisopropylamine (MW: 129.25, 0.758mmol), 163mg (7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid-boron diacetate complex (MW:410.57, 0.397mmol) in 2ml N-methyl-pyrrolidin-2-one. Yield: 70mg, 28.8 %. MS: 641.7 $(M+H)^+$, method ESI^+.

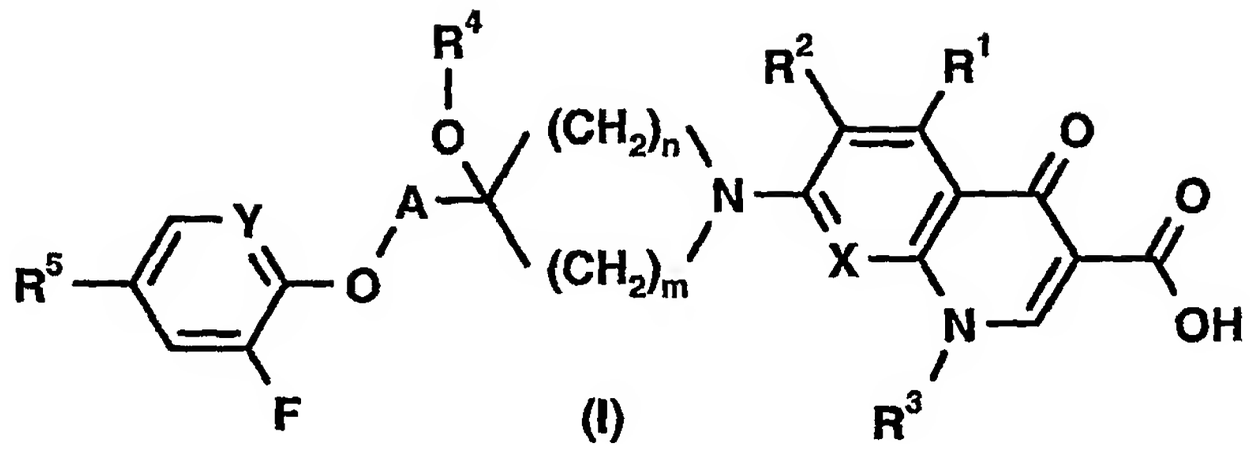
Example 17: 7-(4-{4-[(5S)-5-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenoxymethyl}-4-hydroxy-azepan-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



In analogy to example1 step7 with 98mg 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-[1,8]naphthyridine-3-carboxylic acid (MW: 282.66, 0.348mmol), 138mg N-{(5S)-3-[3-fluoro-4-(4-hydroxy-azepan-4-ylmethoxy)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (MW: 395.43, 0.348mmol), 140mg triethylamine (MW: 101.19, 1.39mmol) and 113mg trimethylchlorsilan (MW: 108.64, 1.04mmol) in 1ml N-methyl-pyrrolidin-2-one. Yield: 150mg, 77 %. MS: 642.7 $(M+H)^+$, 640.7 $(M+H)^-$, Method ESI^+, ESI^-.

Claims

1. Compounds of formula (I)



wherein

A is a C_{1-4} alkylene group, a C_{2-4} alkenylene group, a C_{2-4} alkynylene group or a C_{1-4} heteroalkylene group, all of which may be substituted by one or more hydroxy or amino groups;

X is CR^7 or N;

Y is CR^6 or N;

n is 1, 2 or 3;

m is 1, 2 or 3;

R^1 is H, F, Cl, Br, I, OH, NH_2, an alkyl group or a heteroalkyl group;

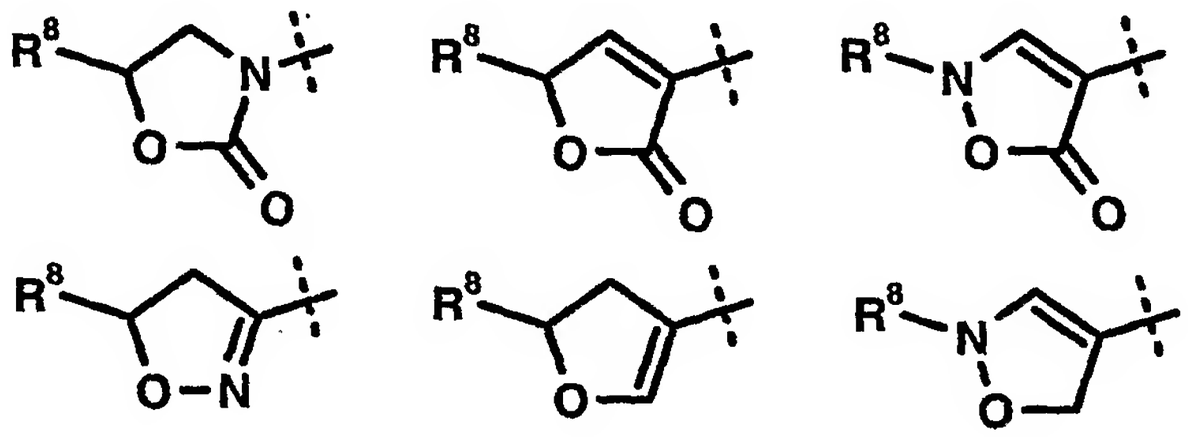
R^2 is H, F or Cl;

R^3 is H, an alkyl group, an alkenyl group, an alkinyl group, a heteroalkyl group, a cycloalkyl group, a heterocycloalkyl group, an aryl group, a heteroaryl

group, an alkylaryl group or a heteroarylalkyl group; all of which may be substituted with one, two or more halogen atoms like F or Cl.

R^4 is hydrogen, a group of formula $PO_3R^9{}_2$ or SO_3R^{10} or a heteroalkyl group carrying at least one OH, NH_2, SO_3R^{10}, $PO_3R^9{}_2$ or COOH group, wherein R^9 is H, alkyl, cycloalkyl, aryl, aralkyl, and wherein R^{10} is H, alkyl, cycloalkyl, aryl, aralkyl,

R^5 is selected from following groups:



R^6 is H, F, Cl or OMe;

R^7 is H, F, Cl, OH, NH_2, an alkyl group or a heteroalkyl group, or

R^3 and R^7 can be linked via an alkylen, an alkenylen or a heteroalkylen group or be a part of a cycloalkylen or heterocycloalkylen group; in case R3 is no H and R5 is no H, F, OH, NH_2 or Cl; and

R^8 is a C_{1-6} heteroalkyl or a heteroarylalkyl group;

or a pharmacologically acceptable salt, solvate, hydrate or formulation thereof.

2. Compounds according to claim 1, wherein R^1 is H.

3. Compounds according to claim 1 or 2, wherein R^2 is F or H.

4. Compounds according to any one of claims 1 to 3, wherein R^3 is an ethyl, a 2-propyl, a C3-C6 cycloalkyl, a phenyl or a pyridyl group, all of which may be substituted by one, two or more fluorine atoms or amino groups.

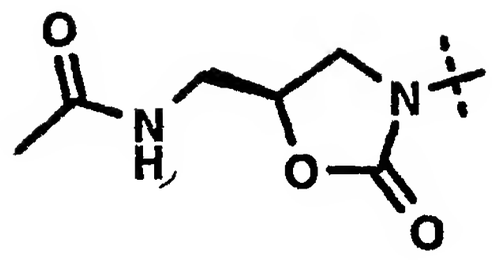
5. Compounds according to any one of claims 1 to 4, wherein R^3 is a cyclopropyl group.

6. Compounds according to any one of claims 1 to 3, wherein R^3 and R^7 together form a group of the formula -O-CH_2-N(Me)- or -O-CH_2-CH(Me)-.

7. Compounds according to any one of claims 1 to 6, wherein R^4 is hydrogen or a group of the formula SO_3H, PO_3H_2, $PO_3(CH_2C_6H_5)_2$, CH_2OPO_3H or $COCH_2CH_2COOH$, or together with the oxygen to which it is bound forms an ester of a naturally occurring amino acid or a derivative thereof.

8. Compounds according to any one of claims 1 to 7, wherein R^8 is a group of the formula -CH_2NHCOCH=CHAryl, - CH_2OHeteroaryl, -CH_2NHSO_2Me, -CH_2NHCOOMe, -CH_2NHCS_2Me, -CH_2NHCSNH_2, -CH_2NHCSOMe or -CH_2NHCOMe.

9. Compounds according to any one of claims 1 to 8, wherein R^5 is a group of the following formula:



10. Compounds according to any one of claims 1 to 9, wherein R^7 is H, F, Cl or a methoxy group which may be substituted by one, two or three fluorine atoms.

11. Compounds according to any one of claims 1 to 10, wherein X is N or CH.

12. Compounds according to any one of claims 1 to 11, wherein Y is CH.

13. Compounds according to any one of claims 1 to 12, wherein A is CH_2 or CH_2CH_2.

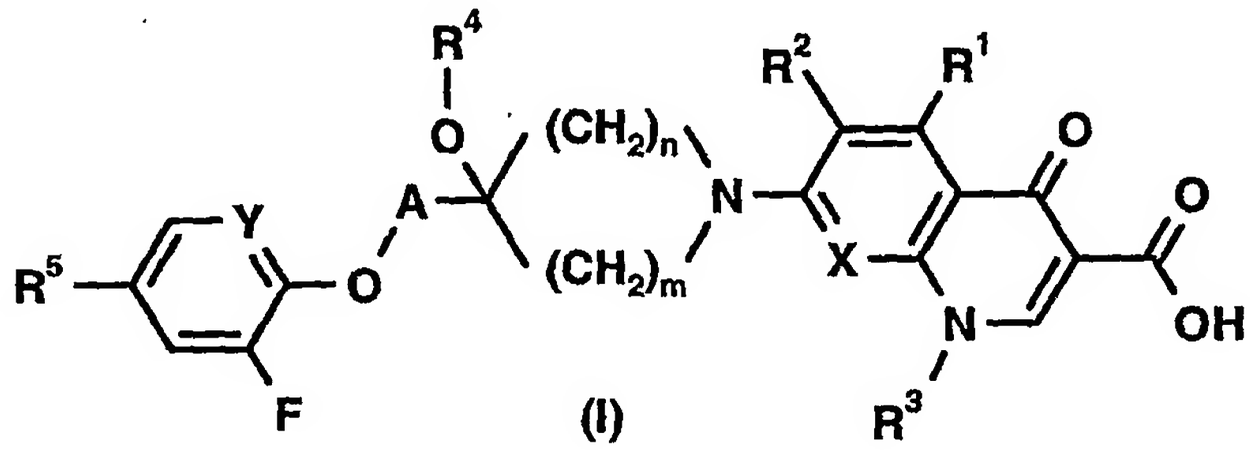
14. Pharmaceutical compositions containing a compound according to any one of Claims 1 to 13 and optionally carriers and/or adjuvants and/or diluents.

15. Pro-drugs, which contain a compound according to any one of Claims 1 to 13 and at least one pharmacologically acceptable protective group.

16. Use of a compound, a pharmaceutical composition or a pro-drug according to any one of Claims 1 to 15 for the manufacture of medicaments for the treatment of bacterial infections.

Abstract

The present invention relates to compounds of the Formula (I) that are useful antimicrobial agents and effective against a variety of multi-drug resistant bacteria:



(I)